IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Application No.	10/736,889	Art Unit:	1642
Applicant:	Georges *et al.*	Examiner:	Lei Yao
Date Filed:	December 15, 2003	Conf. No.	5738
Docket No.	112418.147 (AUR-013US)	Cust. No.	23483
Title:	**Vimentin Directed Diagnostics and Therapeutics For Multidrug Resistant Neoplastic Disease**		

DECLARATION OF ELIAS GEORGES, PH.D.
PURSUANT TO 37 C.F.R. § 1.132

Dear Sir:

In connection with the above-referenced patent application, I, Elias Georges, Ph.D., declare as follows:

1. I received my Ph.D. from McGill University and have spent more than 25 years involved in biochemical research. I have been studying cancer and multidrug resistance in my laboratory research for the better part of my career. I was a post-doctoral researcher at the Ontario Cancer Institute from 1986 to 1991. I am presently an associate professor in the Institute of Parasitology, McGill University. My curriculum vita along with a list of publications, presentations and patents is enclosed hereto as **Attachment A**.

2. I am the co-founder and the President of Aurelium Biopharma, Inc., the assignee of the above-referenced application.

3. I am one of the named inventors of the subject matter described and claimed in the above-referenced application.

4. Our application describes and the claims recite methods of diagnosing and treating multi-drug resistant cancer. In particular, the application describes methods for detecting a neoplastic

or multidrug resistant cell in a patient. The methods generally are directed to a labeled vimentin binding agent that is administered to the patient, and to the detection of the label. The methods also entail the vimentin binding agent specifically binding to cell surface-expressed vimentin present on a neoplastic cell or multidrug resistant cell in the patient.

5. I am also familiar with the Office Action dated August 13, 2007, which states on page four that "the problems encountered in the art and the nature of unpredictability of claimed invention, the *in vivo* experimentation demonstrating that the MDR cells or neoplastic cells are detectable by modified LDL binding to surface expressed vimentin is necessary before one skilled in the art use and practice claimed invention" (see Office Action, pg. 4).

6. Although the cell lines used in my examples are well known models for drug resistance and are recognized in the field of cancer research as being predictive of the *in vivo* behavior of cancer cells, I am providing the results of experiments that we performed further demonstrating that radiolabeled anti-vimentin antibodies target drug resistant tumors *in vivo*. These results in combination with our results from the cell lines show increased cell-surface-expression of vimentin in multi-drug resistant cells establish vimentin as an effective marker for tumors and multidrug resistance *in vivo*.

7. Also, our *in vivo* results establish that all of the vimentin binding agents we disclosed in the specification are effective binders of cell-surface-expressed vimentin. I believe to be the case because our experiments show that one such agent binds to cell-surface-expressed vimentin *in vivo* and the other vimentin binding agents have been previously shown to have specificity for vimentin

8. As will be described below, our results show that the agents and the procedures described in the application can be used to detect neoplastic or multidrug resistant cells *in vivo*. In particular, it is clear for two reasons that the anti-vimentin antibodies used in these experiments specifically bound to cell-surface-vimentin. First, the monoclonal antibodies used in our experiments are specific for vimentin. Second, antibodies do not cross the cell membrane with

any efficiency that would yield detectable results in the following experiments because they are too large to pass through the membrane of the cell or other tissue structures (see U.S. Patent Appl. Pub. No. 20040248201 at paragraph [0014]. It is therefore apparent to me—as it would be to other researchers in my field—that the results described below were obtained due to the specific *in vivo* binding of the radiolabeled anti-vimentin antibodies to *cell-surface-expressed* vimentin. I will now set forth the experiments that we used and the results that we obtained.

9. Our *in vivo* experiments were performed as follows. Athymic, BALB/C nu/nu (nude) mice aged 6-7 weeks old were obtained from Charles River Laboratories. Animals were kept in a specific-pathogen-free unit, housed in cages fitted with filter tops and fed sterile mouse food and water *ad libidum*. Subsequently, SKOV-3 and MDA-MB-231 human cancer cell lines, were harvested in trypsin-versene, re-suspended in serum-free media, and injected subcutaneously into the right flank of irradiated mice (2.0Gy, Co^{60}, 24 hrs prior to cell implantation) for amplification (10^7 cells/200 µl RPMI). When tumors reached 1000 mm^3, the mice were sacrificed, tumors removed and tumor fragments (20-30 mg) were implanted in the right flank of BALB/C nude mice previously irradiated with a gamma-source (2.0Gy, Co^{60}). Tumors were measured using vernier calipers and their volumes (mm3) were determined by the formula: (length x $width^2$)/2.

Murine monoclonal anti-vimentin IgG1 antibody (clone V9) was purified from mouse ascites fluid by protein G and ion exchange chromatography and obtained from Labvision (Fremont, CA, USA). Anti-vimentin antibodies were labeled with $Na^{131}I$ using the IODO-GEN method at Perkin Elmer (Boston, MA, USA). Radiochemical purity was determined by instant thin layer chromatography and indicated that the >95% of the radioiodine was routinely protein bound. Specific activities ranged from 5-10 µCi/µg. Immunoreactivity of radiolabeled anti-vimentin was tested using purified antigen in an ELISA test.

For the determination of anti-tumor activity, tumor-bearing mice were randomized into groups of 6-8 animals when tumors reached 100-200 mm^3. The mean tumor volume of each was not statistically different from the others (analysis of variance). There were 6 treatment groups per tumor model for single dose administration, and 8 groups for the repeated administration study. All mice received an IV injection of potassium iodine in order to saturate the specific binding sites of iodine and protect thyroid function. Mice received a single or repeated IV

injection of ^{131}I-anti-Vimentin antibody or isotypic control. In groups that received taxol, treatment was initiated 24 hours prior to antibody administration in order to allow modulation of antigen number at the surface of tumor cells. The dose of taxol chosen (7.5 mg/kg/injection) is suboptimal and has no demonstrable toxicity in nude mice and when given alone is insufficient to cause complete or partial remission in both ovarian SKOV-3 and breast MDA-MD-231 cancer models.

Mice were monitored daily, and body weight and tumor volumes were measured twice weekly. Mice were sacrificed when the tumor reached a volume of 2000 mm^3. During the course of the study, animals were sacrificed if signs of suffering (cachexia, weakening, difficulty moving or eating), compound toxicity (hunching, convulsions), and tumor growing to 10% body weight or decrease in body weight of 20% or more occurred.

Statistical analyses were performed by taking the average relative tumor volume (RTV) was calculated as the ratio on that day to the volume at the start of the study. The average relative tumor volume within each group was compared over 65 days. All analyses were performed using StatView® software (Abacus concept, Berkeley, USA), using the Bonferroni/Dunn test. Treatment groups were compared with respect to tumor size, relative tumor size over time and tumor doubling time. A p value <0.05 was considered as significant.

10. Figure 2 shows the results of *in vivo* experiments in which mice carrying ovarian SKOV3 xenografts were treated either with of 250 μCi ^{131}I-anti-vimentin, 7.5 mg/kg Taxol (Q7Dx3), a combination of both, or vehicle. SKOV3 is a cell line that is drug resistant. The results show that the anti-vimentin antibody in combination with taxol treatment led to decreased tumor size in mice. The results also establish that anti-vimentin antibodies targeted cell-surface-expressed vimentin *in vivo*, indicating that vimentin binding agents can find and bind cell-surface-expressed vimentin in the complex environment of an organism.

11. Figure 4 shows the results of *in vivo* experiments where mice carrying ovarian SKOV3 xenografts were treated with either a single injection or 3 injections (Q7Dx3) of each of the following: 250 μCi ^{131}I-anti-vimentin alone, taxol alone, 250 μCi ^{131}I-anti-vimentin in combination with 7.5 mg/kg Taxol (Q7Dx3), vehicle, or isotypic control. These studies were

performed to evaluate the effect of repeated injections of the radiolabeled antibody in combination with a suboptimal dose of taxol (7.5 mg/kg, Q7Dx3). The results show that the relative tumor growth inhibition calculated with the median relative tumor volume ("RTV") ranged from 32%-49% between days 42-65 for mice treated with ^{131}I-anti-vimentin at 250 μCi following a Q7Dx3 administration schedule in combination with Taxol at 7.5 mg/kg/injection whereas the relative tumor growth inhibition for mice treated with the antibody alone or Taxol alone was not statistically different than the control group. Tumor volume also decreased significantly in the combination group as compare to anti-vimentin antibody alone near the end of the treatment period. From these results, I show that repeated injections of radiolabeled anti-vimentin antibody further increased the efficacy of a single dose of radiolabeled anti-vimentin in combination with taxol at 7.5 mg/kg.

12. We also performed similar experiments with mice carrying breast MDA-MB-231 cancer cell line xenografts (see Fig. 3). Like SKOV3, these cell lines are clinically resistant lines. The tumor growth in the control (untreated) group was rapid with a tumor quadrupling time of 16 days. A similar rapid growth of xenografts was observed in the isotypic control group (250 μCi, 15 days). Radioimmunotherapy with ^{131}I-anti-vimentin at 250 μCi slowed the rate of tumor growth for approximately 6 days. The combination of ^{131}I-anti-vimentin (250 μCi) and taxol (7.5 mg/kg, Q7Dx3), was significantly more effective in the inhibition of tumor growth when compared with that of each treatment alone. Tumor quadrupling time in this group increased to 31 days. The median survival of animals increased from 39 to 56 days in the combination group. The results show that the anti-vimentin antibody bound to cell-surface-expressed vimentin in the subjects.

13. *In vitro* cell line experiments were performed to determine whether the presence of vimentin on the surface of resistant cells was a consequence of high levels of intracellular protein, MCF-7, a sensitive human breast cancer cell line, was transiently transfected with a pcDNA3.1 vector containing the human vimentin gene. The amount of surface vimentin was then analyzed by intact cell radioimmunoassay using an anti-vimentin antibody and compared to

MCF-7 cells resistant to doxorubicin (MCF-7/AR) which expressed high levels of vimentin at the surface.

As shown in Figure 1, vimentin expression is dramatically increased in multidrug resistant cells ("MCF-7/AR") as compared to drug-sensitive cells ("MCF-7"). These results confirm the results shown in the specification of the application (see, *e.g.*, Figs. 10 and 11). These results also show that vimentin was highly expressed at the surface of MCF-7 cells transfected with pcDNA3.1-vimentin at a level similar to resistant MCF-7/AR cells (Fig. 1). The data indicates that high levels of intracellular vimentin, induced by transfection with a vector containing the gene or by exposure to doxorubicin, result in an overexpression of vimentin and a redistribution of the protein to the surface of the cells.

14. Thus, this data establishes that a vimentin binding agent an anti-vimentin antibody binds *in vivo* specifically to cell-surface-expressed vimentin. Likewise, the other vimentin binding agents disclosed in the specification of our patent application would also bind cell-surface-expressed vimentin *in vivo* with similar efficacy as the anti-vimentin antibody, and that the development and use of the other vimentin binding agents described in the application would not require any particular effort or experimentation. I have come to this conclusion because our experiments show that one such agent binds to cell-surface-expressed vimentin *in vivo* and because the other vimentin binding agents have been previously shown to have specificity for vimentin, as in the case of modified LDL, which has been demonstrated to be a specific binder of vimentin (see Specification, paragraph [0194], citing, Heidenthal, *et al.* (2000) *Biochem. Biophys. Res. Comm.* 267: 49-53). In fact, I would be surprised if the other agents failed to bind to cell-surface-expressed vimentin in light of these results.

15. Also, labeling techniques I used have been described in the specification, and these techniques allow for *in vivo* detection of vimentin (see Specification, paragraphs [0127] and [0138]-[0139]). It would therefore take little experimentation to modify the procedures described in the application such that other labeled vimentin binding agents would be administered to a subject for the purpose of binding to cell-surface-expressed vimentin. The specification also teaches how to detect bound agents *in vivo* (see Specification, paragraphs

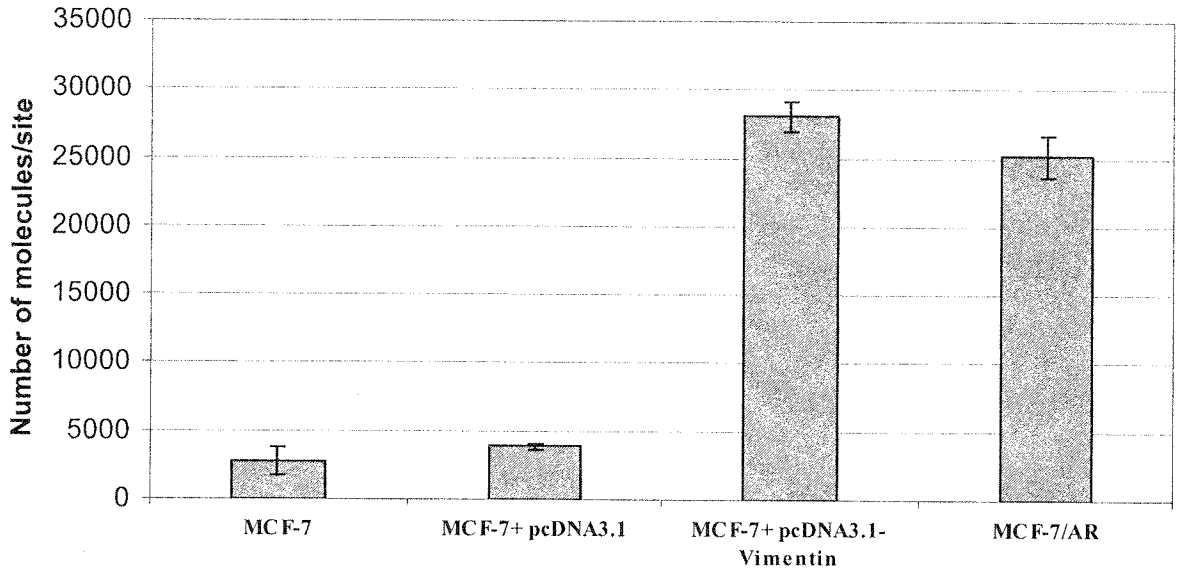
[0127]; [0140]; and [0201]). I, and other researchers in my field, am well aware of techniques for detecting a signal in an organism (see Specification, paragraph [0156], which cites the art for detecting labels *in vivo*). For example, standard X-ray technology is commonly used to detect radiolabeled probes, such as the radiolabeled anti-vimentin antibody that we used in our experiments (see Specification, paragraphs [0140] and [0156]). Therefore, the technology for detecting a labeled probe *in vivo* is not new, and it is most certainly does not require any experimentation or unusual skill to use.

16. In conclusion, the results of our *in vivo* experiments confirm that vimentin binding agents can successfully bind to cell-surface-expressed vimentin in a subject. It is also my opinion that the procedures taught in the specification would require little additional experimentation to use the other labeled vimentin binding agents in a subject. I believe that these opinions would be shared by other researchers in my field when reading the specification and reviewing the results of our experiments.

I further declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true and further that these statements are made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Date: Feb 10, 2008

Elias Georges, Ph.D.


35000
30000
25000
20000
15000
10000
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Number of molecules/site
MCF-7
MCF-7+ pcDNA3.1
MCF-7+ pcDNA3.1-Vimentin
MCF-7/AR

Figure 1

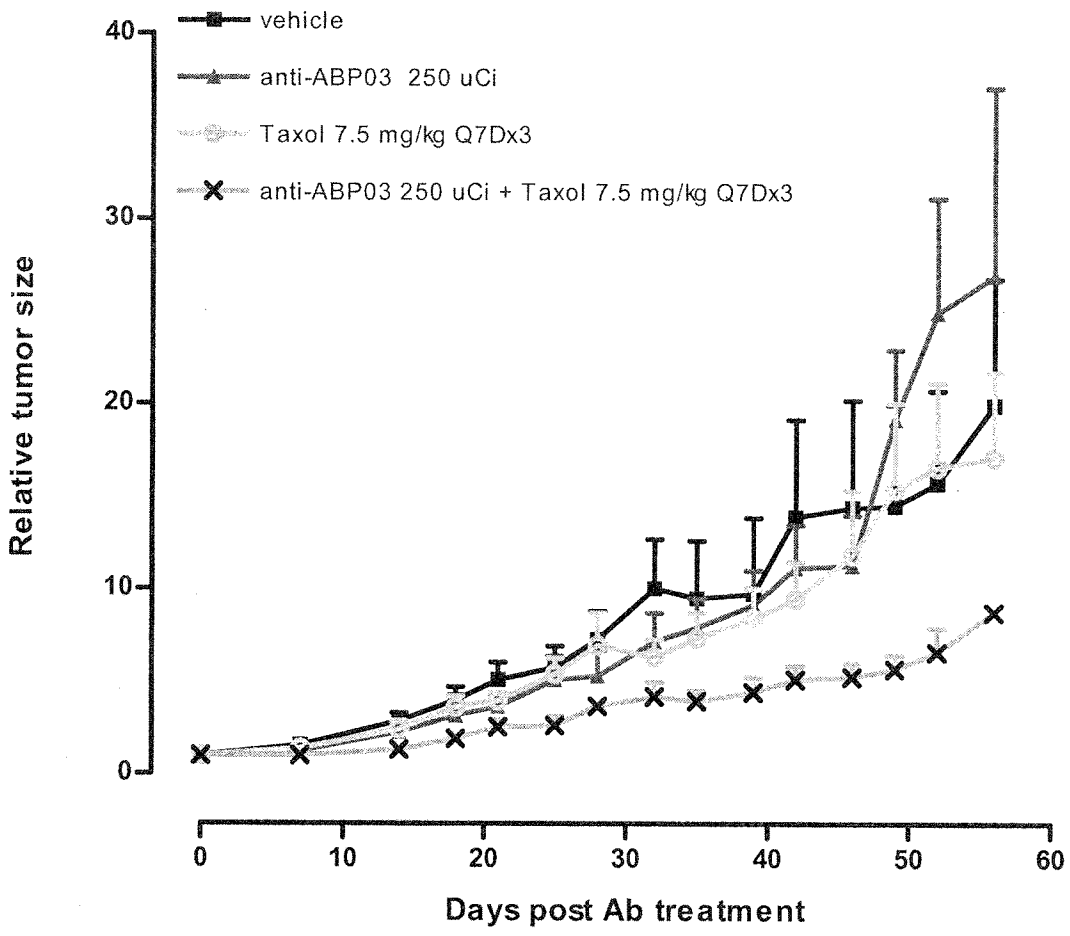
vehicle
anti-ABP03 250 uCi
Taxol 7.5 mg/kg Q7Dx3
anti-ABP03 250 uCi + Taxol 7.5 mg/kg Q7Dx3
Relative tumor size
0
10
20
30
40
0
10
20
30
40
50
60
Days post Ab treatment

Figure 2

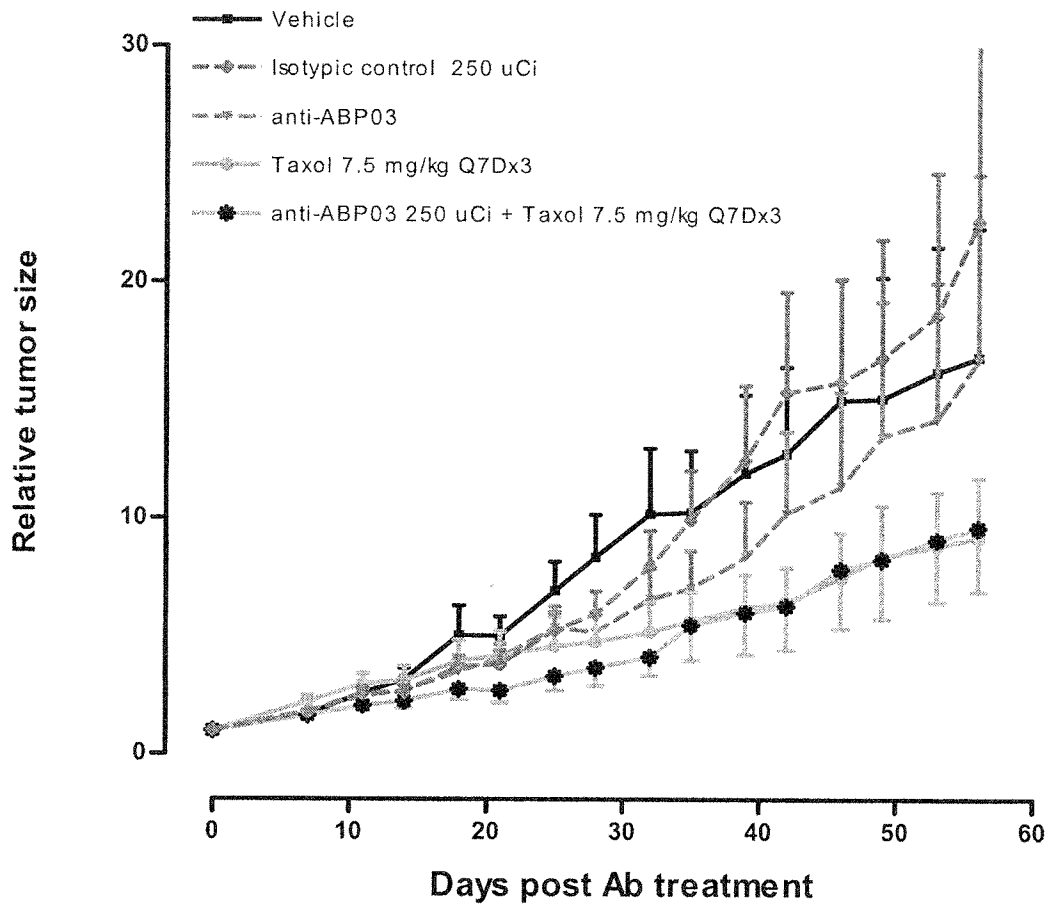
Vehicle
Isotypic control 250 uCi
anti-ABP03
Taxol 7.5 mg/kg Q7Dx3
anti-ABP03 250 uCi + Taxol 7.5 mg/kg Q7Dx3
Relative tumor size
30
20
10
0
0
10
20
30
40
50
60
Days post Ab treatment

Figure 3

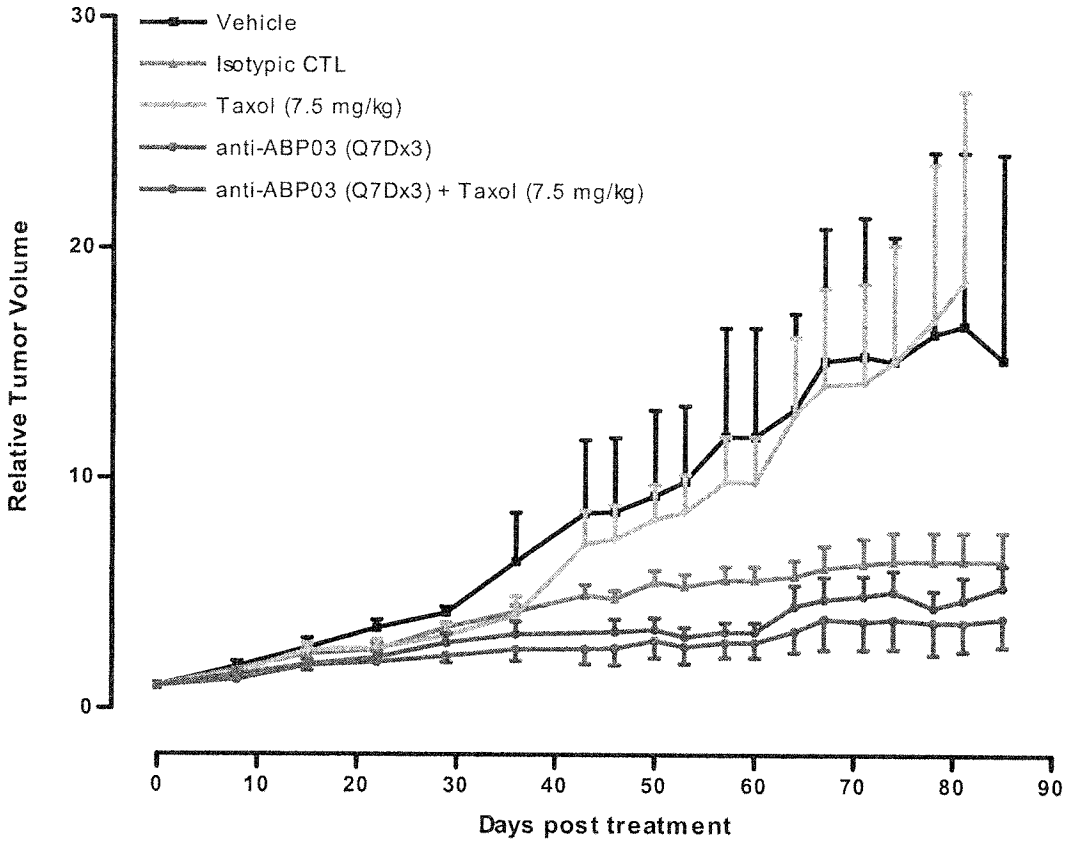
Vehicle
Isotypic CTL
Taxol (7.5 mg/kg)
anti-ABP03 (Q7Dx3)
anti-ABP03 (Q7Dx3) + Taxol (7.5 mg/kg)
Relative Tumor Volume
30
20
10
0
0
10
20
30
40
50
60
70
80
90
Days post treatment

Figure 4

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant:	Georges *et al.*	Art Unit:	1642
Serial No.:	10/736,889	Examiner:	Yao, Lei
Filing Date:	December 15, 2003	Customer No.	23483
Title:	**Vimentin Directed Diagnostics and Therapeutics for Multidrug Resistant Neoplastic Disease**	Conf. No.	5738

ATTACHMENT A

Dr. Elias Georges

EDUCATION

- Ph.D. in Biochemistry
  McGill University, Montreal — 1987
- B.Sc. in Biochemistry
  McGill University, Montreal — 1981

RESEARCH EXPERIENCE

- Research Fellow, Molecular Biology
  Dr. V. Ling, Ontario Cancer Institute — 1986-1991
- Assistant Professor, Institute of Parasitology
  McGill University — 1991-1997
- Associate Professor, Institute of Parasitology
  McGill University — 1997-Present
- Associate Member, Department of Physiology (MTG)
  University of Montreal — 1997-Present
- Associate Professor, Department of Microbiology (Mac)
  McGill University — 1997-Present
- Program Director, Graduate Programs in Biotechnology — 2004-Present

RESEARCH EXPERIENCE

From Nov 1997 to present:

Co-founder, President & CEO/CSO
Aurelium BioPharma Inc.

Management of Aurelium's operations: strategic planning, public presentations, writing of 2 business plans, and all basic operations of a start-up and growing company.

Established and negotiated Out-licensing/collaboration for Breast Cancer Diagnostic with Biosite Inc. (USA Public biotech.) 2006 -

Negotiated and managed $13M R&D collaboration with KS BioMedix (UK public biotech) 2001- 2004

Raising of $14.6 M equity financing through two rounds of financing, from seed to 2nd round.

Director of Aurelium BioPharma Board and SAB 1997- present

Aurelium moved from a concept to three products in pre-clinical & four oncology diagnostics for breast & ovarian cancers.

From Jan 1983 to 1986:
Founder, President
Boutique TIKI Inc. Montreal, Quebec

Founded and managed a high fashion Lady's ware.
Negotiated all business contracts and Bank loans
Trained sales personal

PUBLICATIONS

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Prichard, R., Pouliot, J-F., and Georges, E. Mechanisms of resistance to macrocyclic lactone anthelmintics and reversal of resistance. patent 33,334-00) .

Georges, E. and Wang, Y. P-40 a new member of the Multidrug Resistance proteins in tumor cells. Patent: PCT-2,219,299.

Georges, E. and Bonneau A-M. Subcellular fractions from eucaryotic cells; kits for the rapid subcellular localisation of a protein; and methods of use thereof. Filed in US on December 23, 2002 (serial number to be confirmed)

Georges, E. Protein-protein interactions and methods for identifying interacting proteins and the amino acid sequence at the site of interaction. Patent: 60/134,259.

Georges, E., Bonneau, A.-M., Serfass, L., Dallaire, F., Lachambre, M.-P. and Citton, M. ABP03 detection-based methods for diagnosing and treating damaged cells, neoplastic cells and multi-drug resistance. Patent filed in the U.S. on December 13, 2002. U.S. application serial number: USSN 60/433351.

Georges, E., Bonneau, A.-M., Serfass, L., Dallaire, F., Lachambre, M.-P. and Citton, M. ABP06 detection-based methods for diagnosing and treating damaged cells, neoplastic cells and multi-drug resistance. Patent filed in the U.S. on December 13, 2002. U.S. application serial number: USSN 60/433480.

Georges, E., Bonneau, A.-M., Serfass, L., Dallaire, F., Lachambre, M.-P. and Citton, M. ABP08 detection-based methods for diagnosing and treating damaged cells, neoplastic cells and multi-drug resistance. Patent filed in the U.S. on January 03, 2003 (serial number to come).

REFEREED PAPERS

Karwatski, J. Lincolin, M., and Georges, E. 2005. Hypersensitivity of The Multidrug Resistant Small Cell Lung Cancer Cells, H69/AR, to Buthionine Sulfoximine is Mediated by Apoptosis Resulting from Overexpressing of MRP and Down-Regulation of Bcl-2. (Submitted, Aug 2006)

TRAINEES, GRADUATE STUDENTS AND POSTDOCTORAL FELLOWS

Trainees

Tracy Zordan-Nudo
1991-1993 Research Assistant
Research topic: "Drug-resistance in tumor cells"

Zhi Liu
1992- 1994 Research Assistant
1995- 1996 Research topic: "P-glycoprotein structure-function"

Françoise LHeureux
1994-1995 Research Assistant
1996- 1998 Research topic: "Multidrug-resistance"

Byo Adeeco
2000- 2002 Research Assistant
Research topic: "P40 mediate drug resistance in tumor cells"

Anne Miller Research Assistant
2003-2004 Research topic: "Multidrug resistance"

Jing Lian Research Assistant
2005 - Research topic: "Collateral Sensitivity in drug resistant cells"

Graduate Students

Sharon Rutherford
1992-1994 M.Sc. student; degree awarded
NSERC fellowship
Research topic: "Targeting intracellular proteins using single chain antibodies"

Ying Wang
l993-1998 Ph.D. student.
Funds from NCIC grant
Research topic: "Characterization of novel proteins in multidrug-resistant tumor cells"

Gabriela Certad
1994-1997 M.Sc. student. ***(DEAN'S HONOR LIST THESIS)***
Fundacion Gran Mariscal de Ayacucho and Vollmer Foundation.
Research topic: "Molecular changes in actinomycin D-resistant *Plasmodium falciparum*"

Max Lincoln
1995-1997 M.Sc. student.
Max Stern award from McGill University
Research topic: "Molecular changes in multidrug-resistant cells responsible for the collateral sensitivity to verapamil and other membrane active agent"

Marko Vezmar
1995- 1997 M.Sc. student. ***(DEAN'S HONOR LIST THESIS)***
Funds from WHO and NSERC grants.
Research topic: "Role of P-glycoprotein in the resistance to Chloroquine"

Abrahem Abrahem
1996-1999 M.Sc. student. (fellowship support)
Research topic: "Isolation of proteins containing an ATP Binding Cassette in actinomycin D-resistant *Plasmodium falciparum*."

Roni Daoud
1996- 2001 Ph.D. student ***(DEAN'S HONOR LIST THESIS)***
Funds from NCIC grant
Research topic: "The multidrug resistance protein (MRP) structure and function"

Omar Alqawi
1996-2003 Ph.D. student (fellowship support)
Research topic: "Identification of P-glycoprotein drug binding site"

Joel Karwatski
1998 - Ph.D. student ***(DEAN'S HONOR LIST THESIS)***
Funds from NCI grant
Research topic: "Apoptosis and drug resistance of tumor cells"

Mara Leimanis
2000- Ph.D. Student.
Research topic: Malaria (*P. falciparum)* Proteomics.

Remi-Martin Laberge
2004- Research topic: Characterization of ABCG2 drug binding and transport.

Postdoctoral Fellows

Bakela Nare (Ph.D.)
1991-1993 Funding from NSERC Strategic grant.
Research topic: "Drug-resistance in nematodes and tumor cells"

Xing-Qing Pan (Ph.D.)
1991-1994 Funding from NCIC and NSERC.
Research topic: "Drug-resistance in malaria and tumor cells"

Jean-François Pouliot (Ph.D.)
1994-1996 Funding from NSERC Industry-University Research and Development grant.
Research topic: "Ivermectin-resistance in nematodes and tumor cells"

TEACHING

Course/level	Years Taught	Credits
FDSC 211. Biochemistry I *Course Instructor* (Undergraduates).	1994 - 2001	3 credits
PARA 675. Membrane Proteins in Human Diseases. *Course instructor* (Graduates).	1993 - 2001	3 credits
BTEC 621. Biotechnology Management (Graduates).	Fall 2002 -	3 credits
BTEC 691. Biotechnology Practicum (Graduates)	Winter & Summer 2003 -	3 credits
BTEC 622-625. Research Project	Winter 2005 -	9 credits